"effective fitness" of an arbitrary viral strain evolving under immune pressure in a population. A spearman rank correlation analysis shows that the effective fitness is extremely well correlated with the intrinsic fitness, thus enabling robust inference.

2533-Pos Board B552
Computational Approaches to Systems Biology: Multiple Approaches to *Clostridium Acetobutylicum*
Margaret Hurley.
US Army Research Laboratory, Aberdeen Proving Ground, MD, USA.
Rapid advancements in biotechnology are expected to impact multiple areas of interest to the Army, including decontamination, degradation of toxic chemicals and biofuels. This project is a joint experimental/computational effort to map out the metabolic pathways in *Clostridium acetobutylicum,* and use this information todevelop a systems biology model of this system. This organism has been chosen specifically due to the fact that it has potential application to both biofuel production and nitroaromatic degradation. It is hoped that a systems biology model may provide key information to enhance both of these processes.

2534-Pos Board B553
Using Numerical Modeling to understand the Lipid Biosynthetic Pathway in Chlamydomonas Reinhardtii
Nicole J. Carbonaro, Scott Johnson, Ian F. Thorpe.
University of Maryland, Baltimore County, Baltimore, MD, USA.
A worldwide effort to find renewable alternatives to fossil fuels is underway. Under certain conditions, algae produce large amounts of lipids that can be converted to biodiesel. However, the lipid biosynthetic pathway of algae is not fully understood. Consequently, we use numerical modeling to explore optimization of lipid biosynthesis in the well-studied microalgae *Chlamydomonas reinhardtii.* This goal will be accomplished using deterministic kinetic modeling and flux balance analysis of the lipid biosynthetic pathway. Key parameters of the models will be manipulated in order to predict optimal mechanisms by which higher levels of lipid production can be induced *in vivo*. As an initial step in pursuing these goals, we employ recently developed flux balance analysis models describing the full complement of metabolic processes in *C. reinhardtii* to identify metabolic pathways most relevant to lipid production.

2535-Pos Board B554
Simultaneous Calculation of Dynamical and Equilibrium Properties of Atomistic Systems using an Ensemble of Weighted Trajectories
Daniel M. Zuckerman.
University of Pittsburgh, Pittsburgh, PA, USA.
Equilibrium can be represented as an ensemble of trajectories undergoing dynamics in which detailed balance is maintained. Here, we present results for a simulation protocol based on the "weighted ensemble" (WE) approach of Huber and Kim in which weak coupling between parallel simulations can capture both dynamical and equilibrium properties without statistical bias. The approach is demonstrated in two molecular systems: alanine di-peptide and chignolin, a 10 residue mini-protein. We present results for the mean first passage time between arbitrary states and demonstrate the rapid convergence towards equilibrium for chignolin in comparison to a brute force simulation. Importantly, the analysis of weighted ensemble trajectories does not require states to be defined in advance, and therefore permits the calculation of rates between arbitrary states selected after the simulation is run. We also describe a history-dependent Markov-like formulation to correct for a potentially significant bias in kinetic properties measured from equilibrium WE simulations.

2536-Pos Board B555
Robust and Entrainable Circadian Rhythms from Coupled Catalytic Domains
Michael J. Rust[1], Connie Phong[1], Joseph S. Markson[2], Crystal Wilhoite[1].
[1]University of Chicago, Chicago, IL, USA, [2]Harvard University, Cambridge, MA, USA.
Circadian clocks are ubiquitous biological oscillators that coordinate behavior with the daily cycling of the environment. To ensure synchronization with the environment, the period of the clock must be maintained near 24 hours even as amplitude and phase are altered by input signaling. We show that in a reconstituted circadian system from cyanobacteria these conflicting requirements are satisfied by distinct functions for two domains of the central clock protein KaiC: the C-terminal autokinase domain integrates input signals via the ATP/ADP ratio, and the slow N-terminal ATPase acts as an input-independent timer. We find that phosphorylation in the C-terminal domain followed by an ATPase cycle in the N-terminal domain is required to form the inhibitory KaiB•KaiC complexes that drive the dynamics of the clock. We present a mathematical model in which this ATPase-mediated delay in negative feedback gives rise to a compensatory mechanism that allows a tunable phase and amplitude while ensuring a robust circadian period.

2537-Pos Board B556
Bidirectional Sorting of Self-Propelled Microswimmers in the Presence of Asymmetric Barriers
Jeffrey Drocco, Charles Reichhardt, Cynthia Reichhardt.
Los Alamos National Laboratory, Los Alamos, NM, USA.
We numerically demonstrate bidirectional sorting of flocking particles interacting with an array of V-shaped gates. Each particle aligns with the average swimming direction of its neighbors according to the Vicsek flocking model and experiences additional steric interactions as well as repulsion from the fixed barriers. We show that particles preferentially localize to one side of the barrier array over time and that the direction of this rectification can be reversed by adjusting the particle-particle repulsion radius or the noise term in the equations of motion. These results provide a conceptual basis for isolation and sorting of single-cell and multicellular organisms that move collectively according to flocking-type interaction rules. We additionally present techniques for sorting independent swimmers moving on periodic substrates, including an egg-carton potential and an array of L-shaped barriers.

2538-Pos Board B557
Probing Why Nature may Favor Heterogeneous Myosin Systems through Single Molecule and Systems Level Approaches
Paul F. Egan[1], Philip R. LeDuc[1], Jonathan Cagan[1], Christian Schunn[2].
[1]Carnegie Mellon University, Pittsburgh, PA, USA, [2]University of Pittsburgh, Pittsburgh, PA, USA.
Myosin motor proteins utilize chemical energy and apply mechanical force to actin filaments. We computationally model the emergent interactions of large populations of varied myosin molecules with actin. Two levels are considered: individual myosin molecules and a systems level. We found that heterogeneous systems with a distribution of two different isoforms have unique and sometimes superior performance in comparison to homogeneous systems.
At the single molecule level, we derived a mathematical model based on the swinging lever arm theory for mapping molecular structures to mechano-chemical behaviors. We explored the configurations of four myosin structures as inputs and when all parameters were perturbed individually, they each modulated emergent system behavior differently.
At the systems level, the number and relative concentration of myosin isoforms is varied. The steady-state emergent response of the system (i.e. filament velocity, energy usage, and stability) is determined with respect to varied exogenous forces applied to a moving actin filament. System robustness (ability to operate under a number of different conditions) was examined, and we find that greater robustness requires higher energy usage and larger systems.
When homogeneous and heterogeneous systems are compared, we find superior qualities present in heterogeneous systems. For instance, one heterogeneous system had decreased energy usage at lower velocities (i.e. greater performance) and a higher maximum stable system velocity than any possible homogeneous configuration.
These results provide novel insights for why nature may favor molecularly heterogeneous systems. While myosin heterogeneity in muscles is beneficial because their relative concentrations may adapt over time, our findings suggest that the heterogeneity may also provide increased performance at a specific time. These findings inform the design of future myosin-based technologies, in addition to elucidating the complexity present in natural systems.

2539-Pos Board B558
Modeling Tumor Growth in an Evolving Tissue Structure: A Diffuse Domain Approach
Yao-Li Chuang[1], Vittorio Cristini[1], Ying Chen[2], Xiangrong Li[2], Hermann B. Frieboes[3], John S. Lowengrub[2].
[1]University of New Mexico, Albuquerque, NM, USA, [2]University of California, Irvine, Irvine, CA, USA, [3]University of Louisville, Louisville, KY, USA.
While cancer has been one of the leading causes of human death, predicting and thwarting cancerous tumor development are challenging because of interacting multiscale processes coupled with emerging spatiotemporal patterns that lead to microenvironmental heterogeneity and further to infiltration tendency of tumors. Built upon decades of knowledge toward the biological processes involved in tumor progress, mathematical modeling and analysis have been employed to decipher key mechanisms underlying the sophisticated emerging phenomena in tumor growth observed experimentally and clinically. Among the efforts, we have recently developed a Cahn-Hilliard model of tumor growth at tissue scale, where the Cahn-Hilliard energy described cell aggregation and

phase separation due to differentiated cell-cell adhesion. Various nontrivial emerging patterns resembling observed tumor morphology were identified over the parameter space of our model. However, the previous development and analysis of our model have been implicitly based on the assumption of a homogeneous microenvironmental background and unrestricted boundaries. Most clinically relevant tumors are constrained by particular organ tissue structures that may co-evolve with the progressing tumors and have profound impact on tumor-microenvironment interactions. Here we adopt a recently developed diffuse-domain approach, utilizing the Cahn-Hilliard equation framework we have previously established, to adapt partial-differential-equation models of tumor growth to a co-evolving tissue geometry. We will demonstrate this approach by modeling the growth of lymphoma within a lymph node and ductal carcinoma in situ within mammary ducts.

2540-Pos Board B559

Biochemical Response and the Effects of Bariatric Surgeries on Type 2 Diabetes

Roland E. Allen[1], Tyler D. Hughes[1], Jia Lerd Ng[1], Roberto D. Ortiz[1], Michel Abou Ghantous[2], Othmane Bouhali[2], Abdelilah Arredouani[3].
[1]Texas A&M University, College Station, TX, USA, [2]Texas A&M University at Qatar, Doha, Qatar, [3]Qatar Biomedical Research Institute, Doha, Qatar.

A general method is introduced for calculating the biochemical response to pharmaceuticals, surgeries, or other medical interventions. This method is then applied in a simple model of the response to Roux-en-Y-gastric bypass (RYGB) surgery and related procedures. We specifically address the amazing fact that glucose homeostasis is usually achieved immediately after RYGB surgery, long before there is any appreciable weight loss. This result is usually attributed to a dramatic increase in an incretin, glucagon-like peptide 1 (GLP-1), but our model indicates that this mechanism alone is not sufficient to explain the largest declines in glucose levels or measured values of the homeostatic model assessment insulin resistance (HOMA-IR). The most robust additional mechanism would be production of a substance which opens an insulin-independent pathway for glucose transport into cells, analogous to the established insulin-independent pathway associated with exercise.

2541-Pos Board B560

Modeling Cluster Formation by Multivalent Interacting Proteins: Nephrin-Nck-NWasp Signaling in the Foot Process of Kidney Podocytes

Cibele V. Falkenberg, Michael L. Blinov, Leslie M. Loew.
U.Conn. Health Center, Farmington, CT, USA.

Intracellular function is often defined by clusters consisting of multiple multivalent molecules. Studying these clusters represents a significant challenge because of the potentially infinite number of cluster compositions and the intermediate complexes that are formed while clusters are formed. To make the matter worse, many clusters are very liquid, the affinities of the many bimolecular site interactions are quite modest, implying that off-rates are relatively rapid. Thus, we need efficient methods to predict the average composition of these ensembles, characterizing number of molecules of different types, number of bonds per different molecule types, and other parameters defining the size and structure of the cluster. Here we present a stochastic steady state algorithm for multivalent interacting molecules to determine cluster compositions and sizes based on probability that each type of binding site is bound. The advantage of the method is in its efficiency: tracking the formation of the cluster over time would require computation of binding and unbinding steps; instead, we identify a distribution of cluster compositions at the time point of interest based on the pairwise binding probability among multiple sites within interacting molecules. The method is applied to the system Nephrin-Nck-NWasp. The interaction between these three multi-domain molecules is required for maintenance of the podocyte foot processes cytoskeleton, the key cellular structure in the kidney slit diaphragm filtration system. The weak individual site pair affinities and estimated nephrin concentrations at the slit diaphragm by themselves would be insufficient to promote actin polymerization. We use our method to address how the multi domain and cooperative mechanisms could provide such function. Supported by NIH grants TR01DK087650 and P41GM103313.

Synaptic Transmission

2542-Pos Board B561

Synaptic Vesicle Capture by Intact CaV2.2 Channels

Fiona K. Wong, Qi Li, Elise F. Stanley.
Toronto Western Research Institute, Toronto, ON, Canada.

The fusion of synaptic vesicles (SVs) at the presynaptic transmitter release face is gated by Ca^{2+} influx from nearby voltage gated calcium channels (CaV). Our early functional studies argued that the CaV and SV are linked by a molecular anchor or 'tether' and recent studies have proposed a direct cytoplasmic link to the channel distal C terminal. In order to explore CaV-SV binding we developed an in vitro assay, termed SV-PD, to test for capture of purified, intact SVs. Antibody-immobilized presynaptic or expressed CaV2.2 channels but not plain beads, IgG or pre-blocked antibody successfully captured SVs, as assessed by Western blot for a variety of protein markers. SV-PD was also observed with a distal C terminal fusion protein, C3strep, supporting involvement of this CaV region. Our results favor the model where presynaptic CaV can tether SVs directly, independently of the surface membrane.

2543-Pos Board B562

Optical Modulation of Neurotransmission

Mercè Izquierdo-Serra[1], Dirk Trauner[2], Artur Llobet[3], Pau Gorostiza[1].
[1]Insitute for Bioengineering of Catalonia, Barcelona, Spain, [2]Ludwig-Maximilians-Universität, Munich, Germany, [3]Bellvitge Institute for Biomedical Research (IDIBELL), Barcelona, Spain.

The computational properties of an isolated neuron have been analyzed in detail by postsynaptic activation with caged compounds. However, new tools are needed to manipulate neurotransmission at individual synapses in order to understand how a neuron integrates physiological stimuli received from presynaptic neurons within a circuit. Here we describe a method to control neurotransmitter exocytosis at the presynaptic compartment by using a light-gated glutamate receptor (LiGluR). In chromaffin cells, LiGluR supports exocytosis by means of a calcium influx that is comparable to voltage-gated calcium channels. Presynaptic expression of LiGluR in hippocampal neurons enables direct and reversible control of neurotransmission with light, and allows modulating the firing rate of the postsynaptic neuron with the wavelength of illumination. This method constitutes an important step toward the determination of the complex transfer function of individual synapses.

2544-Pos Board B563

Molecular Mechanisms of Synchronous Synaptic Transmission

Sunny Jones, Shyam Krishnakumar, Daniel Kummel, James Rothman.
Yale University, New Haven, CT, USA.

Complexin and Synaptotagmin work in concert to couple the SNARE-mediated membrane fusion machinery to the triggering signal i.e. influx of Ca^{2+} ions. The SNARE assembly process is arrested at a very late stage by Complexin, to prevent spontaneous fusion events and the Complexin clamp is reversed by Synaptotagmin in a Ca^{2+}-dependent manner to synchronize the neurotransmitter release. To understand the mechanistic details of this process, we developed a Nanodisc based system, which allows us to generate trans-SNARE complexes under soluble conditions. SNAREs on Nanodisc assemble but do not fuse due to the topological constraints placed by the Nanodiscs. We employed a VAMP construct (VAMP-4X) which carries mutations in the C-terminal hydrophobic layers that prevent assembly of this region with the t-SNARE to accurately recreate the pre-fusion SNARE complex between two bilayers that mimic the vesicle-bilayer junction in docked vesicles. Fluorescence analysis show that the Synaptotagmin binds to the pre-fusion SNAREpin between the two bilayer under Ca^{2+} free conditions and the primary interaction is such that SNARE assembly or Complexin binding does not affect it. Calcium- additions triggers a very rapid co-penetration of the Ca^{2+}-binding loops of both C2 domains into the bilayer, with somewhat higher preference to the bilayer containing t-SNAREs and this partitioning could be further augmented by the addition of PIP2. However, Synaptotagmin maintains its position on the SNARE complex during the whole process. Recent data has shown that Complexin arrests fusion by blocking the complete assembly of SNAREpins in adjacent complexes i.e. a trans-clamping interaction. Our results suggest a simple, one-step physical mechanism by which Synaptotagmin could trigger the reversal of the trans-Complexin clamp and activate fusion, in response to Calcium.

2545-Pos Board B564

Calcium Triggered Membrane Penetration of Synaptotagmin may Provide the Driving Force to Reverse the Complexin Clamp

Shyam Krishnakumar, Sunny Jones, Daniel Kummel, James Rothman.
Yale University, New Haven, CT, USA.

Synaptic proteins, Complexin and Synaptotagmin act in sync to achieve the speed and the accuracy of the synaptic transmission. Complexin (CPX) arrests the SNARE assembly in the late stages promoting the docking of the synaptic vesicles at the active zone and along with Synaptotagmin, the calcium sensor, synchronizes the fusion of these vesicles with the influx of calcium ions following the nerve impulse. Recently, we obtained the first X-ray crystal structure representing the clamped state of SNAREpin at the docked vesicles, which shows that Complexin arrests fusion by blocking the complete assembly of the v-SNAREs in the adjacent SNARE complex. This trans- interaction generates an unusual zigzag array of half-zippered (pre-fusion) SNARE complexes between the two bilayers. Here we present experiments using a novel Nanodisc-based system that mimics a vesicle-bilayer junction that suggests